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STATE-OF-THE-ART REVIEW

Mineralocorticoid Antagonism in Heart Failure

Established and Emerging Therapeutic Role

Joycie Chang, BA,[a,b] Andrew P. Ambrosy, MD,[c,d] Orly Vardeny, PharmD, MS,[e,f] Harriette G.C. Van Spall, MD, MPH,[g,h] Robert J. Mentz, MD,[i] Andrew J. Sauer, MD[a,b]

HIGHLIGHTS

- MRAs for HF are underused due to safety concerns including hyperkalemia and sexual side effects.
- Current evidence supports using steroidal MRAs for HFrEF but is inconclusive regarding HFmrEF and HFpEF.
- Nonsteroidal MRAs show promise for HF due to superior specificity, potency, and tolerability.
- Future trials will evaluate steroidal and nonsteroidal MRAs for reducing heart failure events.

ABSTRACT

The pathophysiology of heart failure (HF) is related to the overactivation of the mineralocorticoid receptor, leading to fluid retention and adverse myocardial remodeling. Although mineralocorticoid receptor antagonists (MRAs) are recommended for the treatment of heart failure with reduced ejection fraction (HFrEF), they remain underused due to adverse effects such as hyperkalemia; and their efficacy is controversial in heart failure with mildly reduced ejection fraction (HFmrEF) and heart failure with preserved ejection fraction (HFpEF). Recent trials in people with diabetes and kidney disease have supported the use of nonsteroidal MRAs in reducing HF-related morbidity and mortality and have fewer side effects than their steroidal counterparts. The efficacy and safety of nonsteroidal MRAs have not been tested in HF and are currently being evaluated in additional clinical trials. This review comprehensively examines the current data regarding MRAs for HF and the future direction of nonsteroidal MRA research while exploring the causes of MRA underutilization. (JACC Heart Fail. 2024;■:■–■) © 2024 by the American College of Cardiology Foundation.

From the [a]Saint Luke's Mid America Heart Institute, Kansas City, Missouri, USA; [b]University of Missouri-Kansas City School of Medicine, Kansas City, Missouri, USA; [c]Department of Cardiology, Kaiser Permanente San Francisco Medical Center, San Francisco, California, USA; [d]Division of Research, Kaiser Permanente Northern California, Pleasanton, California, USA; [e]Minneapolis VA Center for Care Delivery and Outcomes Research, Minneapolis, Minnesota, USA; [f]University of Minnesota Department of Medicine, Minneapolis, Minnesota, USA; [g]Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada; [h]Baim Institute for Clinical Research, Boston, Massachusetts, USA; and the [i]Division of Cardiology, Department of Medicine, Duke University School of Medicine, Durham, North Carolina, USA.

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SHOUT
SHARE
IT

ABBREVIATIONS AND ACRONYMS

ACEI = angiotensin-converting enzyme inhibitor

ARB = angiotensin-receptor blocker

CKD = chronic kidney disease

eGFR = estimated glomerular filtration rate

HFmrEF = heart failure with mildly reduced ejection fraction

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

LVEF = left ventricular ejection fraction

MR = mineralocorticoid receptor

MRA = mineralocorticoid receptor antagonist

NT-proBNP = N-terminal pro-B-type natriuretic peptide

UACR = urinary albumin-to-creatinine ratio

Heart failure (HF) affects more than 56.2 million people worldwide and poses a significant burden to the aging population.[1] Chronic HF is characterized by the overactivation of the renin-angiotensin-aldosterone system. In particular, the mineralocorticoid aldosterone contributes substantively to the pathophysiology of HF. Current evidence-based therapy for HF includes the use of mineralocorticoid receptor antagonists (MRA), which have been shown to prevent many of the deleterious effects of aldosterone. Well-powered randomized clinical trials have demonstrated the efficacy of MRAs for treating heart failure with reduced ejection fraction (HFrEF), with an apparent reduction in mortality and readmissions among patients who receive MRAs.[2]

Despite a strong level of evidence, MRAs remain underused for HFrEF for reasons including hyperkalemia and gynecomastia/breast pain related to blockage of the androgen receptor.[3,4] The Swedish Health Registry observed that only 40% of patients with HFrEF duration ≥6 months received MRA therapy.[5] EVOLUTION HF (Utilization of Dapagliflozin and Other Guideline Directed Medical Therapies in Heart Failure Patients: A Multinational Observational Study Based on Secondary Data) showed that only 5.1% of those with HF in Japan, Sweden, and the United States reached the target dose of MRAs, and 42.2% discontinued the drug within a 12-month period.[6] Canadian data show that even after interventions meant to increase the use of guideline-directed medical therapy in high-risk patients, uptake of MRAs remains low at <32%.[7] Similarly, low and static rates of MRA use in HF are observed in the United States. The U.S. Get With The Guidelines-HF study from 2005-2007 reported 32% use of MRAs,[8] and the more recent CHAMP-HF (Change the Management of Patients with Heart Failure) study reported 33% use of MRAs.[9]

Although there are clinician concerns of hyperkalemia leading to underutilization of MRAs, research has shown that SGLT2 inhibitors or angiotensin receptor/neprilysin inhibitors may mitigate the risk of hyperkalemia in patients congruently taking MRAs.[10-12] Potassium-binding agents have also been shown to reduce rates of hyperkalemia when taken with MRAs.[13]

STEROIDAL MRAs IN HFrEF

Aldosterone has an essential role in the pathogenesis of HF. Elevated aldosterone levels contribute to endothelial dysfunction and promote myocardial fibrosis and pathological remodeling by interacting with mineralocorticoid receptors (MRs) in the heart and blood vessels.[14] In the kidney, aldosterone exacerbates hypervolemia and congestion by upregulating tubular sodium and water reabsorption, and excretion of potassium and magnesium.[15] Steroidal MRAs directly block the MR but tend to have affinity for other steroid receptors including androgen and progesterone receptors, leading to adverse effects including gynecomastia, impotence, and menstrual irregularities.[16] Randomized clinical trials have demonstrated the efficacy of MRAs in treating HF (**Central Illustration**). Three landmark trials—RALES (Randomized Aldactone Evaluation Study), EPHESUS (Eplerenone Post-myocardial infarction Heart failure Efficacy and Survival Study), and EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure)—have shown that MRA use in HFrEF results in significant reductions in cardiovascular death and hospitalization for HF compared with placebo (**Table 1**). RALES was the first large, randomized, double-blind, placebo-controlled clinical trial to evaluate the safety and efficacy of MRA for the treatment of HF.[17] Before its publication, angiotensin-converting enzyme inhibitors (ACEIs) were largely thought to completely inhibit aldosterone production, and physicians often believed the use of MRAs with ACEIs was contraindicated due to severe hyperkalemia.[17] In fact, the 1995 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for HF management only recommended MRAs in the setting of hypokalemia secondary to diuretic use and cautioned against dangerous hyperkalemia when used in combination with ACEIs or large doses of oral potassium.[18] The findings of RALES played a large role in increasing robust data and clinician comfort for the use of MRAs for HF. The study assessed the efficacy of 25 mg of the MRA spironolactone vs placebo in 1,663 patients with NYHA functional class III or IV and an ejection fraction ≤35% who were being treated with an ACEI and a loop diuretic for the primary endpoint of death from any cause with a mean follow-up period of 24 months. The study reported a 30% reduction in the risk of death (relative risk [RR]: 0.7 [95% CI:

CENTRAL ILLUSTRATION Steroidal vs Nonsteroidal MRA in Clinical Trials

Steroidal MRA

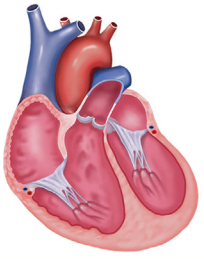
- Spironolactone and eplerenone
- Function as partial agonists
- Lower potency
- Dose-related increase in potassium
- Less selectivity
- More sexual side effects

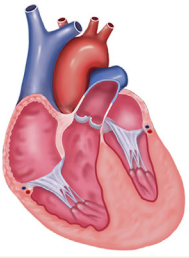
Nonsteroidal MRA

- Finerenone, esaxerenone, balcinerenone
- Function as inverse agonists or partial antagonists
- Higher potency
- Lower rates of hyperkalemia
- Greater selectivity
- Minimal to no sexual side effects

Clinical Trials With MRA

Ejection Fraction Category: HFrEF | HFmrEF | HFpEF





Completed (HFrEF)

- **RALES:** Reduction in death from any cause with spironolactone
- **EMPHASIS-HF:** Reduction in CVD + HHF with eplerenone
- **ARTS-HF:** Similar reduction in NT-proBNP and rates of hyperkalemia with finerenone vs eplerenone

Completed (HFmrEF/HFpEF)

- **TOPCAT:** No difference in CVD + HHF + aborted cardiac arrest between spironolactone and placebo
- **FINEARTS-HF:** Reduction in CVD + HF events with finerenone

Ongoing (HFrEF)

- **FINALITY-HF:** Finerenone in patients intolerant to or ineligible for steroidal MRA for CVD + HF events

Ongoing (HFmrEF/HFpEF)

- **SPIRIT-HF:** Spironolactone vs placebo for CVD + HHF
- **SPIRRIT:** Spironolactone + usual care vs usual care alone for CVD + HHF
- **REDEFINE-HF:** Finerenone vs placebo in patients hospitalized for acute HF for CVD + HF events
- **Polydiuretic Therapy for Heart Failure With Preserved Ejection Fraction: A Pilot Trial:** Eplerenone + empagliflozin + bumatenide vs empagliflozin alone for cardiorenal health measures

Ongoing Clinical Trials Enrolling Patients With Any Ejection Fraction

- **CONFIRMATION-HF:** Early initation of finerenone + empagliflozin for patients with acute HF vs usual care for a composite of death from any cause, HF events, and quality of life
- **BalanceD-HF:** balcinerenone + dapagliflozin vs dapagliflozin only for a composite of CVD + HHF + HF events

Chang J, et al. JACC Heart Fail. 2024;■(■):■-■.

Nonsteroidal mineralocorticoid receptor antagonists (MRAs) possess obvious advantages compared to older steroidal MRAs. There is strong evidence for the use of steroidal MRAs to treat heart failure with reduced ejection fraction (HFrEF). Current and future clinical trials will provide important data on the safety and efficacy of steroidal and nonsteroidal MRAs for the treatment of heart failure with mildly reduced ejection fraction (HFmrEF)/heart failure with preserved ejection fraction (HFpEF). Results of completed clinical trials and anticipated outcomes of ongoing trials are reported using the primary outcomes identified. Green dots indicate trials that met the primary outcome. Red dots indicate trials that did not meet the primary outcome. White dots indicate ongoing trials. CVD = cardiovascular death; HHF = hospitalizations for heart failure; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

TABLE 1 Summary of Landmark for MRA Use in HFrEF

Trial Name and Year	Drug Studied	N	Mean Follow-Up, y	Inclusion Criteria: LVEF%, NYHA	Primary Endpoint	Number of Events (Treatment vs Placebo)	RR or HR of Primary Outcome	Rate of Adverse Events
RALES, 1999	Spironolactone 25 mg vs placebo	1,663	2	LVEF <35%, NYHA functional class III or IV	Death from any cause	284 (35%) vs 386 (46%)	RR: 0.7 (0.60-0.82)	Serious hyperkalemia (serum potassium ≥6.0 mmol/L): 1% in placebo group vs 2% in spironolactone group; gynecomastia or breast pain:1% of men in placebo group vs 10% of men in the spironolactone group
EMPHASIS-HF, 2011	Eplerenone 25 mg increased after 4 weeks to 50 mg once daily vs placebo	2,737	1.75	LVEF <35%, NYHA functional class II	Composite of death from cardiovascular causes or hospitalization for heart failure	249 (18.3%) vs 356 (25.9%)	HR: 0.63 (0.54-074)	Serious hyperkalemia (serum potassium ≥6.0 mmol/L): 1.9% in placebo group vs 2.5% in eplerenone group; gynecomastia or breast disorders: 1.0% of men in placebo group vs 0.7% of men in the eplerenone group

RALES (Randomized Aldactone Evaluation Study) and EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) are 2 landmark clinical trials that provided much of the evidence for the safety and efficacy of mineralocorticoid receptor antagonists (MRAs) for heart failure with reduced ejection fraction (HFrEF). Ultimately, these trials helped establish MRAs as an integral medication in the guideline-directed medical therapy for HFrEF.

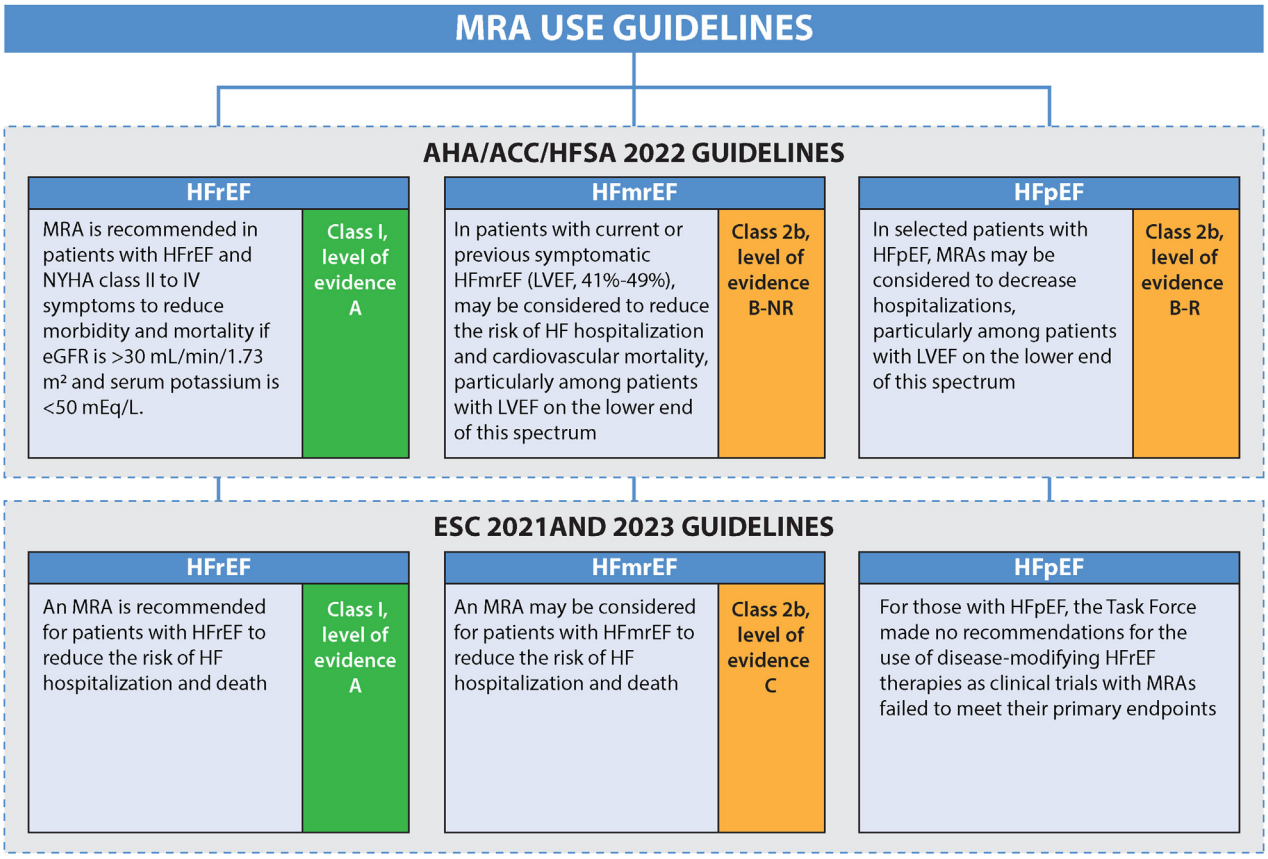
LVEF = left ventricular ejection fraction; RR = relative risk.

0.60-0.82]; $P < 0.001$) in patients treated with spironolactone. Patients treated with spironolactone also experienced significant reductions in the risk of death from cardiac causes (RR: 0.69 [95% CI: 0.58-0.82]; $P < 0.001$), hospitalization from cardiac causes (RR: 0.7 [95% CI: 0.59-0.82]; $P < 0.001$), and improvements in the NYHA functional class ($P < 0.001$). Although the median potassium concentrations increased by 0.30 mmol/L in the spironolactone group, which was significantly higher compared with the placebo group ($P < 0.001$), there was only a 2% incidence of severe hyperkalemia (defined as ≥6.0 mmol/L) in the spironolactone group compared with 1% in the placebo group. Gynecomastia also contributed to study drug discontinuation, with 10% of men reporting gynecomastia or breast pain compared with 1% of men in the placebo group.

In a population-based time-series analysis of the trends in the rate of spironolactone prescriptions and the rate of hospitalization for hyperkalemia in ambulatory patients before and after the publication of RALES, Juurlink et al[4] report that the rate of hospital admissions involving a diagnosis of hyperkalemia in patients with HF who were prescribed spironolactone and ACEIs tripled after the publication of RALES, resulting in an incidence of 11.0 per 1,000. This significant increase in the rate of hospital admission for hyperkalemia and subsequent in-hospital death after the publication of RALES persisted after adjustment for temporal changes in the prescription rates of other commonly used drugs that can cause hyperkalemia. Possible theories for this rise in hyperkalemia and associated hospital admissions include lack of close monitoring of potassium levels, neglecting baseline attributes that predispose patients to hyperkalemia, and using inappropriately high doses of spironolactone.[4,12,19]

In EMPHASIS-HF, the safety and efficacy of eplerenone were also evaluated in patients with mild HF symptoms. EMPHASIS-HF randomized 2,737 patients with NYHA functional class II HF symptoms and an ejection fraction of ≤30% (or, if >30% to 35%, a QRS duration of >130 ms on electrocardiography) receiving standard therapy for HFrEF to eplerenone starting at 25 mg and increased to 50 mg after 4 weeks vs placebo for a median follow-up period of 21 months. Eplerenone was shown to reduce the primary outcome of death from cardiovascular causes or first hospitalization for HF by 37% (HR: 0.63 [95% CI: 0.54-0.74]; $P < 0.001$). Treatment with eplerenone also resulted in a lower risk of hospitalization (HR: 0.77 [95% CI: 0.67-0.88]; $P < 0.001$). Eplerenone was well-tolerated in patients with mild HF symptoms; the most common adverse events were hyperkalemia and gynecomastia/breast disorders. The median potassium level increased by 0.16 mmol/L in the eplerenone group compared with 0.05 mmol/L in the placebo group. The rates of severe hyperkalemia were increased, but not statistically significant, between treatment groups (potassium >5.5 mmol/L: 11.8% for eplerenone and 7.2% for placebo group; potassium

FIGURE 1 Guidelines for the Use of MRAs in HFrEF, HFmrEF, and HFpEF


MRA USE GUIDELINES
AHA/ACC/HFSA 2022 GUIDELINES
HFrEF
MRA is recommended in patients with HFrEF and NYHA class II to IV symptoms to reduce morbidity and mortality if eGFR is >30 mL/min/1.73 m² and serum potassium is <50 mEq/L.
Class I, level of evidence A
HFmrEF
In patients with current or previous symptomatic HFmrEF (LVEF, 41%-49%), may be considered to reduce the risk of HF hospitalization and cardiovascular mortality, particularly among patients with LVEF on the lower end of this spectrum
Class 2b, level of evidence B-NR
HFpEF
In selected patients with HFpEF, MRAs may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum
Class 2b, level of evidence B-R
ESC 2021AND 2023 GUIDELINES
HFrEF
An MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death
Class I, level of evidence A
HFmrEF
An MRA may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death
Class 2b, level of evidence C
HFpEF
For those with HFpEF, the Task Force made no recommendations for the use of disease-modifying HFrEF therapies as clinical trials with MRAs failed to meet their primary endpoints

Guidelines published by the American Heart Association (AHA), American College of Cardiology (ACC), and Heart Failure Society of America (HFSA) in 2023 and the European Society of Cardiology (ESC) in 2021 and the corresponding updates in 2023. eGFR = estimated glomerular filtration rate; HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist.

>6.0 mmol/L: 2.5% for eplerenone and 1.9% for placebo group).[20]

Based on the results of these landmark trials, the current ACC/AHA/Heart Failure Society of America (HFSA) and European Society of Cardiology (ESC) guidelines strongly recommend the use of MRAs with a high level of evidence for treating HFrEF[21,22] (Figure 1). Given the incidence of hyperkalemia among patients treated with MRAs, the AHA/ACC/HFSA also recommends close monitoring of potassium, renal function, and diuretic dosing at 1 week, 4 weeks, and then every 6 months after initiating or intensifying MRA to minimize the risk of hyperkalemia and renal insufficiency.

STEROIDAL MRAs IN HEART FAILURE WITH MILDLY REDUCED EJECTION FRACTION AND HEART FAILURE WITH PRESERVED EJECTION FRACTION

Although there is strong evidence for using MRAs in HFrEF, the clinical trial data for their use in heart failure with mildly reduced ejection fraction (HFmrEF) and heart failure with preserved ejection fraction (HFpEF) are less robust. TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist), a double-blinded, placebo-controlled randomized clinical trial, showed that MRAs did not mitigate these endpoints in HFpEF.

TOPCAT enrolled 3,445 patients with clinically symptomatic HF with a left ventricular ejection fraction (LVEF) of ≥45%, controlled systolic blood pressure, and no hyperkalemia.[23] Participants were randomized to spironolactone 15 mg initially and increased to 45 mg after 4 months or placebo. The primary outcome evaluated was a composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of HF. After a median follow-up period of 3.3 years, spironolactone did not significantly reduce the primary outcome event compared with placebo (HR: 0.89 [95% CI: 0.77-1.04]; $P = 0.14$). Treatment with spironolactone did not result in significant differences in the risk of death from cardiovascular causes (HR: 0.90; $P = 0.35$). It resulted in modest reductions in the risk of hospitalization for HF (HR: 0.83; $P = 0.04$) compared with placebo.

Analyses stratified by geographic region revealed that participants from America had significantly higher rates of the primary outcome than those from Russia and Georgia (HR: 3.96 [95% CI: 3.22-4.88]; $P < 0.001$). Post hoc analyses of the regional differences revealed that those in the Americas experienced a substantial reduction in the primary outcome with spironolactone treatment (HR: 0.82 [95% CI: 0.69-0.98]), whereas participants from Russia and Georgia did not experience significant reductions in the primary outcome with treatment (HR: 1.10 [95% CI: 0.79-1.51]).[24] When comparing the 2 groups, there were significant differences in nearly every important baseline characteristic between the 2 groups. Interestingly, the rates of hyperkalemia were also significantly different between geographic regions. Those in the Americas experienced a much higher incidence of hyperkalemia in the spironolactone group compared with placebo (OR: 3.46 [95% CI: 2.62-4.56]; $P < 0.001$); however, those in Georgia and Russia did not experience this relationship (OR: 1.30 [95% CI: 0.95-1.77]; $P = 0.10$). Analyses of the concentration of canrenone, an active metabolite of spironolactone, also suggest that the rates of adherence in the Georgia/Russian cohort may be less than reported. In analyses of 366 patients from the TOPCAT trial (206 patients from the United States and Canada, and 160 patients from Russia), canrenone concentrations were undetectable in 30% of participants from Russia vs 3% from the United States and Canada ($P < 0.001$). Moreover, there was a significant correlation between the doses of spironolactone and the concentration of canrenone that was found in participants from the United States and Canada, but was absent in those from Russia.[25] In Georgia, the severity of HF was much milder than that of patients from the Americas, which could also explain why spironolactone had little effect in this population. These regional differences in baseline characteristics, hyperkalemia rates, canrenone concentration, HF severity, proportion of ischemic heart disease, and primary outcome rates present additional confounders for the 2 regional groups. In addition to regional differences, post hoc, non-prespecified analyses of sex differences in outcomes and responses in TOPCAT also demonstrated that women derive greater treatment benefit with spironolactone compared with men with regard to all-cause mortality (HR: 0.66; $P = 0.01$), with a significant interaction between sex and treatment arm (P for interaction = 0.02).[26]

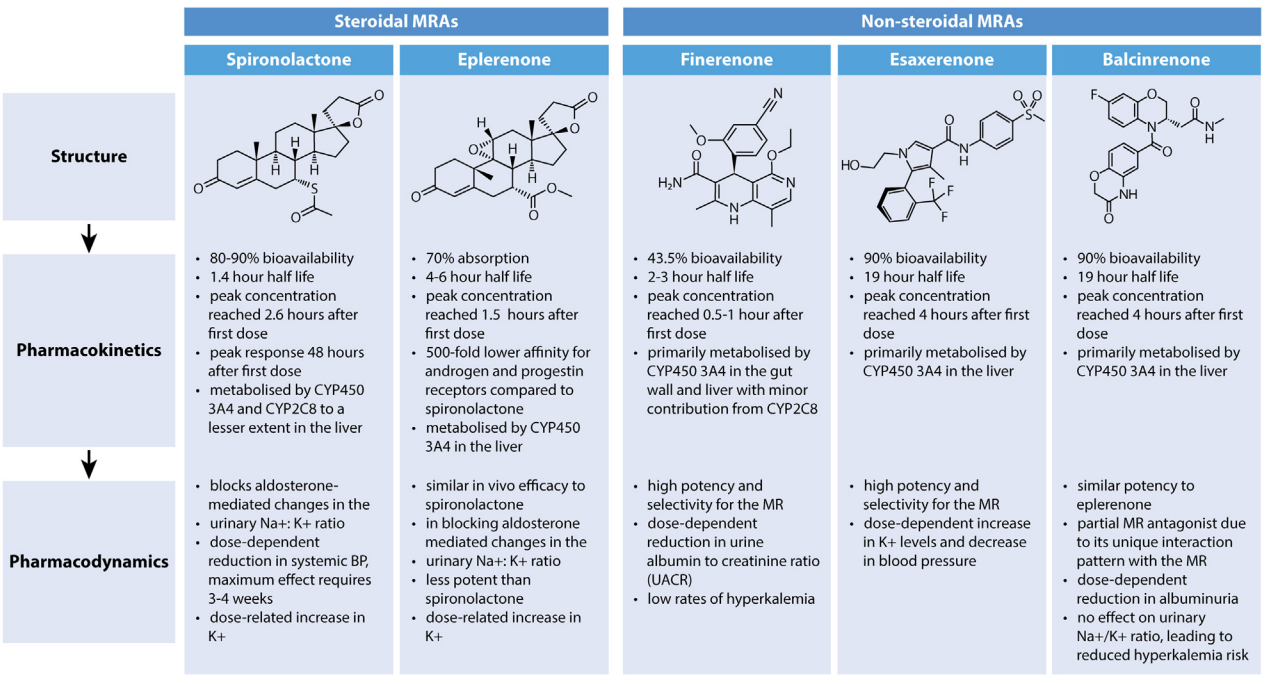
Whereas TOPCAT was designed to examine the effect of aldosterone antagonism on clinical outcomes in HFpEF, other randomized controlled trials (RCTs) have examined the effect of MRAs on surrogate outcomes. In particular, Aldo-DHF (Aldosterone Receptor Blockade in Diastolic Heart Failure) also examined the impact of spironolactone in HFpEF in a European cohort.[27] This double-blinded, placebo-controlled RCT enrolled 422 participants in Germany and Austria, with 213 randomized to spironolactone and 209 randomized to placebo with a median follow-up period of 11.9 months. Participants were 50 years or older with NYHA functional class II or III, LVEF ≥50%, echocardiographic evidence of diastolic dysfunction or atrial fibrillation at presentation, and a maximum exercise capacity (peak VO_2) of 25 mL/kg/min or less. The primary endpoints evaluated were change in diastolic function as determined by echocardiogram (E/e′ ratio) at 12 months and the change in maximum exercise capacity (peak VO_2 on cardiopulmonary exercise testing) at 12 months. The study reported that spironolactone significantly improved diastolic function compared with placebo ($P < 0.001$ for the difference between groups), whereas peak VO_2 increased in both groups but was not significantly different between groups. Spironolactone was well-tolerated, and the rates of severe hyperkalemia were similar among groups (<1% for spironolactone and placebo groups).

Considering the TOPCAT results and the relative lack of other well-powered clinical trials for the use of MRAs in HFpEF, the AHA/ACC/HFSA and ESC guidelines provide a weak recommendation for the use of MRAs in HFmrEF and HFpEF.

NONSTEROIDAL MRAs

Despite the clear benefit of steroidal MRAs such as spironolactone and eplerenone in treating HFrEF, limitations such as hyperkalemia still presented a

FIGURE 2 Steroidal vs Nonsteroidal MRAs


Steroidal vs Non-steroidal MRAs
Steroidal MRAs
Non-steroidal MRAs
Spironolactone
Eplerenone
Finerenone
Esaxerenone
Balcinrenone
Structure
Pharmacokinetics
• 80-90% bioavailability
• 1.4 hour half life
• peak concentration reached 2.6 hours after first dose
• peak response 48 hours after first dose
• metabolised by CYP450 3A4 and CYP2C8 to a lesser extent in the liver
• 70% absorption
• 4-6 hour half life
• peak concentration reached 1.5 hours after first dose
• 500-fold lower affinity for androgen and progestin receptors compared to spironolactone
• metabolised by CYP450 3A4 in the liver
• 43.5% bioavailability
• 2-3 hour half life
• peak concentration reached 0.5-1 hour after first dose
• primarily metabolised by CYP450 3A4 in the gut wall and liver with minor contribution from CYP2C8
• 90% bioavailability
• 19 hour half life
• peak concentration reached 4 hours after first dose
• primarily metabolised by CYP450 3A4 in the liver
• 90% bioavailability
• 19 hour half life
• peak concentration reached 4 hours after first dose
• primarily metabolised by CYP450 3A4 in the liver
Pharmacodynamics
• blocks aldosterone-mediated changes in the
• urinary Na+: K+ ratio
• dose-dependent reduction in systemic BP, maximum effect requires 3-4 weeks
• dose-related increase in K+
• similar in vivo efficacy to spironolactone
• in blocking aldosterone mediated changes in the
• urinary Na+: K+ ratio
• less potent than spironolactone
• dose-related increase in K+
• high potency and selectivity for the MR
• dose-dependent reduction in urine albumin to creatinine ratio (UACR)
• low rates of hyperkalemia
• high potency and selectivity for the MR
• dose-dependent increase in K+ levels and decrease in blood pressure
• similar potency to eplerenone
• partial MR antagonist due to its unique interaction pattern with the MR
• dose-dependent reduction in albuminuria
• no effect on urinary Na+/K+ ratio, leading to reduced hyperkalemia risk

Nonsteroidal mineralocorticoid receptor antagonists (MRAs) possess different structures and pharmacokinetic and pharmacodynamic properties compared with their steroidal counterparts. These differences play key roles in the greater potency, higher selectivity for the mineralocorticoid receptor (MR), and reduced risk for hyperkalemia typically seen with nonsteroidal MRA use. BP = blood pressure.

significant obstacle to the widespread use of MRAs, sparking efforts to develop selective, nonsteroidal MRAs. Nonsteroidal MRAs exhibit many differences from their steroidal counterparts (Figure 2). In particular, nonsteroidal MRAs exhibit greater selectivity for the MR, which mitigates the antiandrogenic and progestogenic effects seen in steroidal MRAs that also have activity at other steroid receptors. Nonsteroidal MRAs also have a lower risk of hyperkalemia and function as inverse agonists, which results in reduced co-regulator recruitment compared with steroidal MRAs, which function as partial agonists.[3]

Finerenone is a nonsteroidal MRA approved by the Food and Drug Administration to treat patients with chronic kidney disease (CKD) associated with type 2 diabetes. It demonstrates greater specificity for the MR than eplerenone and spironolactone, and has little cross-reactivity with other steroid receptors and ion channels. Finerenone's potency is comparable to spironolactone, as evidenced by its significant reductions in nuclear translocation and cofactor and RNA polymerase recruitment compared with spironolactone.[3] Finerenone's distinct method of receptor binding and activity as an inverse agonist appears to have critical downstream effects, such as greater inhibition of profibrotic gene expression compared with spironolactone and eplerenone, which act as partial agonists.[28]

NONSTEROIDAL MRAs IN KIDNEY DISEASE. The FIDELIO-DKD (Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and Diabetic Kidney Disease) trial was the first large RCT to examine the safety and efficacy of finerenone.[29] FIDELIO-DKD was a double-blind, placebo-controlled trial that enrolled participants with type 2 diabetes and CKD, defined as either moderately elevated albuminuria (urinary albumin-to-creatinine ratio [UACR] 30 to <300) and an estimated glomerular filtration rate (eGFR) of 25-60 mL/min/1.73 m^2 of body surface area or severely elevated albuminuria (UACR 300-5,000) and an eGFR of 25 to 75 mL/min/1.73 m^2 of body-surface area who were treated with an ACEI or angiotensin-receptor blocker (ARB) at

the maximum tolerated dose. Key exclusion criteria included patients with a clinical diagnosis of chronic HFrEF and persistent symptoms (NYHA functional class II to IV) at run-in visit (Class 1A recommendation for MRAs). The primary outcome was a composite of kidney failure, a sustained decrease of at least 40% in the eGFR from baseline for at least 4 weeks, or death from renal causes. After a median follow-up period of 2.6 years, the incidence of the primary outcome was significantly lower with finerenone than with placebo (HR: 0.82 [95% CI: 0.73-0.93]). Of note, patients in the finerenone group experienced significantly lower risk of cardiovascular events (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure) (HR: 0.86 [95% CI: 0.75-0.99]). Finerenone was well-tolerated and had a similar rate of serious adverse events compared with placebo (31.9% vs 34.3%). Although the rate of serious hyperkalemia was higher in the finerenone group (1.6%) compared with placebo (0.4%), the rate was lower compared with the rate of hyperkalemia with steroidal MRAs in patients with HF as previously described.

Following FIDELIO-DKD, FIGARO-DKD (Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease) investigated the effects of finerenone in preventing cardiovascular events and mortality in people with type 2 diabetes and CKD, expanding the application of finerenone into the cardiovascular space.[30] FIGARO-DKD was a double-blinded, placebo-controlled trial that enrolled participants with similar criteria as FIDELIO-DKD (type 2 diabetes and CKD defined as UACR 30 to <300 mg/g and eGFR 25-90 mL/min/1.73 m^2, *or* UACR 300-5,000 mg/g and eGFR ≥60 mL/min/1.73 m^2 treated with maximum doses of ACEIs or ARBs, and excluding those with a clinical diagnosis of chronic HFrEF and persistent symptoms [NYHA functional class II-IV] at the run-in visit) and randomized them to finerenone or placebo of differing doses depending on eGFR at baseline. The incidence of the primary outcome, a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for HF, was lower in the finerenone group than in the placebo group (HR: 0.87 [95% CI: 0.76-0.98]). Like FIDELIO-DKD, the rates of serious hyperkalemia were also much lower than previously reported with steroidal MRAs (0.7% with finerenone, 0.1% with placebo).

The efficacy of finerenone in preventing cardiovascular and kidney-related morbidity and mortality was supported by prespecified pooled analyses of FIDELIO-DKD and FIGARO-DKD as described in FIDELITY. Regarding cardiovascular benefits, pooled results from FIDELIO-DKD and FIGARO-DKD showed that the composite cardiovascular outcomes (time to cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization from HF) occurred in 12.7% of participants receiving finerenone compared with 14.4% in those receiving placebo (HR: 0.86 [95% CI: 0.78-0.95]). A reduced incidence of hospitalization from HF was the main driver of cardiovascular benefit with finerenone, with a RR reduction of 22% compared with placebo (HR: 0.78 [95% CI: 0.66-0.92]). Regarding renal benefits, pooled analyses showed that the use of finerenone was associated with a 30% reduction in the risk of sustained (≥57%) decrease in eGFR on top of optimization of ACEI or ARB therapy as well as a 20% RR reduction in the risk of end-stage kidney disease compared with placebo.[31] The results of this pooled analysis also support the use of finerenone in reducing the risk of cardiovascular and renal complications across a broad spectrum of CKD and type 2 diabetes, underscoring the clinical emerging role of nonsteroidal MRA.

Emerging preclinical data also suggest there might be a role for finerenone in the treatment of nondiabetic CKD. In murine models that underwent nephrectomy to induce CKD, treatment with finerenone prevented left ventricular diastolic dysfunction and increased tissue perfusion associated with a reduction in cardiac fibrosis.[32]

NONSTEROIDAL MRAs IN HF. Whereas FIDELIO-DKD and FIGARO-DKD assessed the safety and efficacy of finerenone in patients with diabetic kidney disease, ARTS-HF (MinerAlocorticoid Receptor antagonist Tolerability Study-Heart Failure) was a randomized, double-blind, phase 2b clinical trial that compared finerenone to eplerenone in patients with chronic HFrEF and type 2 diabetes and/or CKD (eGFR of >30 mL/min/1.73 m^2 in patients with type 2 diabetes and 30-60 mL/min/1.73 m^2 in patients without type 2 diabetes). The primary outcome assessed was the proportion of patients with a decrease in plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) level of >30% from baseline to day 90. After treating patients with up-titrations of either study drug depending on serum potassium levels, the proportion of patients with a >30% decrease in NT-proBNP levels from baseline was similar in the finerenone and eplerenone groups. In secondary analyses, a composite endpoint of death from any cause, cardiovascular hospitalization, or emergency presentation for worsening chronic HF until day 90 was evaluated. The incidence of the composite endpoint was lower in all finerenone dose subgroups compared with

eplerenone except for the finerenone 2.5- to 5-mg group, with the finerenone 10- to 20-mg dose group experiencing the greatest reduction in the composite outcome (HR: 0.56 [95% CI: 0.35-0.90]). These findings suggest that finerenone at higher doses and titrations may play a role in reducing HF severity and disease burden. The side effect profile of finerenone and eplerenone in ARTS-HF was similar to previous studies of these drugs. The incidence of hyperkalemia (defined as potassium ≥5.6 mmol/L) at any instance during the study occurred in 4.3% of patients and had a balanced distribution among all treatment groups.[33]

Esaxerenone is a potent blood pressure-lowering nonsteroidal MRA that has been approved for the treatment of hypertension in Japan.[34] Esaxerenone has a longer half-life, higher absolute bioavailability, higher selectivity for the MR, greater potency, and fewer adverse effects such as hyperkalemia than steroidal MRAs like spironolactone and eplerenone.[3] RCTs have demonstrated that esaxerenone may have more significant and immediate renoprotective effects compared with placebo in those with type 2 diabetes[35] and improved myocardial remodeling in those with HFpEF as indicated by a significant decrease in left ventricular mass index and BNP levels.[36]

Balcinrenone, or AZD9977, is a selective partial agonist of the MR that has been shown to have cardiorenal protection and reduced propensity to cause hyperkalemia in vitro (**Figure 2**). In uninephrectomized male rats who were administered aldosterone and fed a high-salt diet, balcinrenone resulted in a dose-dependent reduction in UACR comparable to eplerenone. Balcinrenone was also shown to be renoprotective in murine models of diabetic nephropathy, as balcinrenone inhibited kidney disease progression and reduced urine albumin excretion, similar to the effect seen with eplerenone.[37]

The recently concluded, phase 2b, randomized, double-blind, active-controlled MIRACLE (Study to Evaluate the Efficacy, Safety, and Tolerability of Oral AZD9977 and Dapagliflozin Treatment in Patients With Heart Failure and Chronic Kidney Disease) trial provides initial data regarding the use of balcinrenone (AZD9977) in the setting of HF and CKD in humans. This trial enrolled participants who have NYHA functional class II-III HF, LVEF <60%, NT-proBNP ≥300 pg/mL, and eGFR ≥30 and ≤60 mL/min/1.73^2 and UACR ≥30 mg/g and <3,000 mg/g, and will evaluate the efficacy and safety of AZD9977 at 3 different doses in combination with dapagliflozin compared with dapagliflozin alone after 12 weeks. The measured primary endpoints include the percent change from baseline in UACR at 12 weeks, the number of adverse events, and changes from baseline in serum potassium and eGFR. Recently published results showed that there was no significant reduction in UACR from baseline to 12 weeks after treatment with any dose of balcinrenone + dapagliflozin compared with dapagliflozin + placebo. Dapagliflozin-plus-placebo-adjusted geometric mean percentage changes in UACR from baseline to week 12 were −33.6% (95% CI: −62.5% to 17.6%) in the balcinrenone 15-mg group, −11.8% (95% CI: −52.0% to 62.6%) in the 50-mg group, and −36.1% (95% CI: −64.9% to 16.1%) in the 150-mg group.[38]

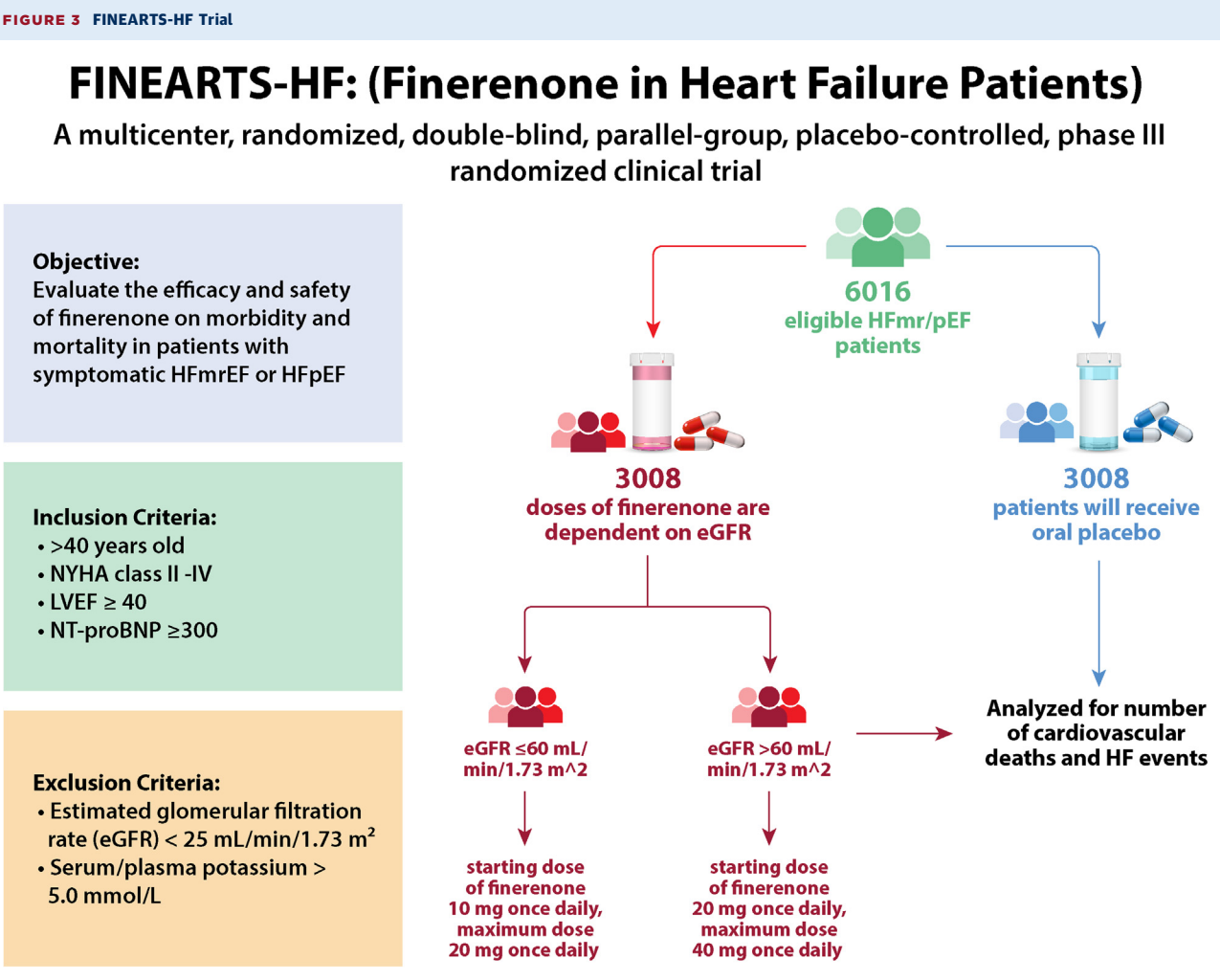
REAL-WORLD USE OF NONSTEROIDAL MRAs. Although nonsteroidal MRAs demonstrate significant benefit in preclinical and emerging clinical trials, their real-world application may be limited by their expensive cost compared with generic steroidal MRA alternatives.[3] For now, steroidal MRAs should remain an integral role in the treatment of cardiorenal disease due to their cost effectiveness. More data, such as head-to-head clinical trials and post-marketing efficacy studies of steroidal vs nonsteroidal MRAs, are needed to establish a clear advantage of nonsteroidal MRAs before there is widespread clinical use.

FUTURE OF MRAs

With evidence supporting improved clinical outcomes with nonsteroidal MRAs in those with type 2 diabetes and CKD with and without HF, ongoing studies are investigating the role of nonsteroidal MRAs to reduce the morbidity and mortality associated with HF, given their strong cardiorenal benefits (**Figures 3 to 5**).

FUTURE MRA TRIALS ACROSS THE ENTIRE EJECTION FRACTION SPECTRUM. CONFIRMATION-HF (Combined Efficacy and Safety of an Early, Intensive, Management Strategy With Finerenone and SGLT2 [sodium-glucose co-transporter 2] Inhibitor in Patients Hospitalized With Heart Failure) (**Figure 4**) is a randomized, controlled, open-label clinical trial evaluating the early, intensive management strategy utilizing a combination of finerenone plus an SGLT2 inhibitor compared with the standard of care in patients hospitalized with HF. Those who are ≥18 years of age, currently hospitalized, or recently discharged with the primary diagnosis of HF, and with elevated NT-proBNP (≥1,000 pg/mL) will be administered finerenone and empagliflozin or standard of care for 6 months. The clinical benefit will be evaluated using a hierarchical composite assessed by the win ratio and includes the time to death from any cause, number of HF events, time to first HF event, and a difference of 5

FIGURE 3 FINEARTS-HF Trial


FINEARTS-HF: (Finerenone in Heart Failure Patients)
A multicenter, randomized, double-blind, parallel-group, placebo-controlled, phase III randomized clinical trial
Objective:
Evaluate the efficacy and safety of finerenone on morbidity and mortality in patients with symptomatic HFmrEF or HFpEF
Inclusion Criteria:
• >40 years old
• NYHA class II -IV
• LVEF ≥ 40
• NT-proBNP ≥300
Exclusion Criteria:
• Estimated glomerular filtration rate (eGFR) < 25 mL/min/1.73 m²
• Serum/plasma potassium > 5.0 mmol/L
6016
eligible HFmr/pEF patients
3008
doses of finerenone are dependent on eGFR
3008
patients will receive oral placebo
eGFR ≤60 mL/ min/1.73 m^2
eGFR >60 mL/ min/1.73 m^2
starting dose of finerenone 10 mg once daily, maximum dose 20 mg once daily
starting dose of finerenone 20 mg once daily, maximum dose 40 mg once daily
Analyzed for number of cardiovascular deaths and HF events

FINEARTS-HF (Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients With Heart Failure) is the only ongoing/future finerenone clinical trial that has finished enrollment. The trial will evaluate the use of finerenone vs placebo in patients with HFmrEF or HFpEF and is expected to conclude in 2024. NT-proBNP = N-terminal pro-B-type natriuretic peptide; other abbreviations as in Figures 1 and 2.

points or greater on the Kansas City Cardiomyopathy Questionnaire-Total Symptom Score (KCCQ-TSS). Other safety endpoints include the number of serious adverse events and the number of adverse events leading to discontinuation of either study drug. CONFIRMATION-HF (A Study to Determine the Efficacy and Safety of Finerenone and SGLT2i in Combination in Hospitalized Patients With Heart Failure; NCT06024746) will be important in establishing data on the potential benefit of SGLT2 inhibitors in reducing hyperkalemia when used in combination with MRAs, as SGLT2 inhibitors have been shown to reduce the odds of developing hyperkalemia.[39]

BalanceD-HF (Study to Evaluate the Effect of Balcinrenone/Dapagliflozin in Patients With Heart Failure and Impaired Kidney Function; NCT06307652) is a phase 3 clinical trial that will provide information regarding the safety and efficacy of balcinrenone with an SGLT2 inhibitor compared with SGLT2 inhibitor only (Figure 5). The study will enroll participants with NYHA functional class III-V HF, any LVEF value within the last 12 months, NT-proBNP >300 pg/mL, an eGFR ≥20 to <60 mL/min/1.73 m², and serum/plasma potassium ≥3.5 mmol/L and ≤5.0 mmol/L. Participants will be randomized to 1 of 3 treatment arms: balcinrenone 15 mg + dapagliflozin 10 mg, balcinrenone 40 mg + dapagliflozin, or placebo + dapagliflozin 10 mg, and the primary endpoint is the time to first occurrence of any components of a composite of cardiovascular death, HF hospitalization, and HF event

FIGURE 4 Future Finerenone Trials Currently or Not Yet Enrolling

	OBJECTIVE	INCLUSION CRITERIA	EXCLUSION CRITERIA	INTERVENTION	PRIMARY ENDPOINTS	SECONDARY ENDPOINTS
REDEFINE-HF	To provide data on safety and efficacy of the early initiation of finerenone in patients with HFmrEF/HFpEF hospitalized due to acute HF	• Patients who are hospitalized due to acute HF with LVEF ≥ 40%	• eGFR<25 mL/min/1.73m^2 or serum/plasma potassium >5.0 mmol/L at screening	Placebo + Standard of Care vs. Finerenone 10 mg, 20 mg or 40 mg + Standard of Care	• Total cardiovascular deaths and HF events	• Time to death from any cause • Change in quality of life*
CONFIRMATION-HF	To provide data on efficacy and safety for simultaneous initiation of finerenone and SGLT2i in patients hospitalized or recently discharged for acute decompensated HF	• Patients hospitalized due to HF or recently discharged • NTproBNP ≥ 1000 pg/mL or BNP ≥ 250 pg/mL	• Diagnosis of type 1 diabetes or prior history of diabetic ketoacidosis	Standard of Care vs. Finerenone + emplagliflozin	• Composite of death from any cause, number of HF events, time to first HF event, and changes in quality of life*	• Number of deaths from any cause and total HF events • Change in KCCQ score • Number of HF events
FINALITY-HF	To broaden the evidence base for the efficacy and safety fo finerenone in the HFrEF population in patients who are unable to take steroidal MRAs	• Symptomatic HFrEF • Not on steroidal MRA due to history of intolerance, contraindication, or ineligibility for treatment	• Treatment with non-steroidal MRA	Placebo + Standard of Care vs. Finerenone + Standard of Care	• Time of first occurence of cardiovascular death or HF event	• Change in KCCQ score • Time to first occurence of composite kidney endpoint • Time to death from any cause

*measured by Kansas City Cardiomyopathy Questionnaire (KCCQ-TSS)

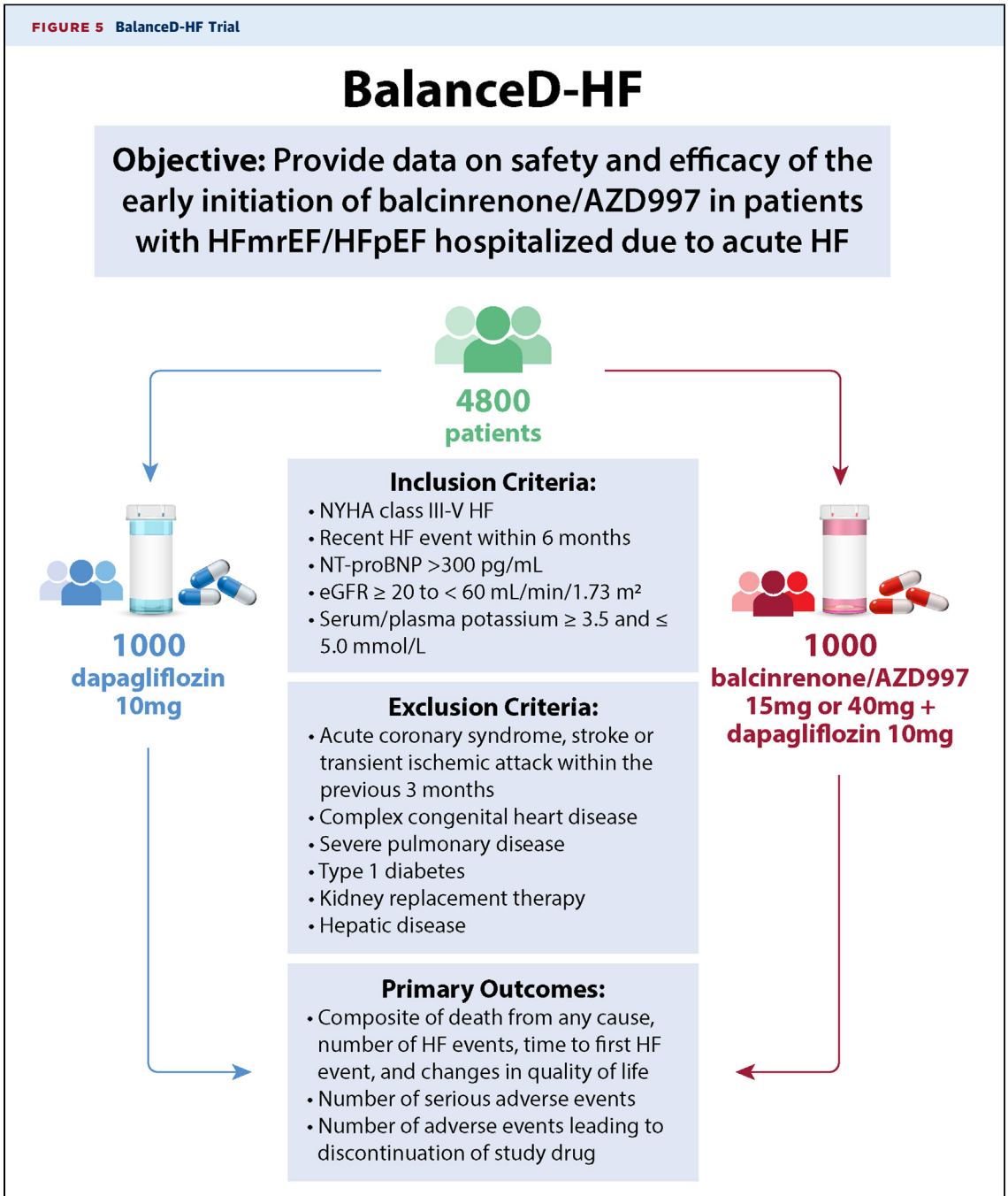
REDEFINE-HF (Randomized Trial to Determine the Efficacy and Safety of Finerenone on Morbidity and Mortality Among Heart Failure Patients With Left Ventricular Ejection Fraction Greater Than or Equal to 40% Hospitalized Due to an Episode of Acute Decompensated Heart Failure), CONFIRMATION-HF (Combined Efficacy and Safety of an Early, Intensive, Management Strategy With Finerenone and SGLT2 [sodium-glucose co-transporter 2] Inhibitor in Patients Hospitalized With Heart Failure), and FINALITY-HF (FINerenone on clinical efficacy and safety in patients with Heart Failure and reduced ejection fraction) are ongoing or future clinical trials involving finerenone that are either currently enrolling or have not begun enrollment. KCCQ = Kansas City Cardiomyopathy Questionnaire; other abbreviations as in Figures 1, 2, and 3.

without hospitalization. BalanceD-HF is expected to conclude in 2027.

FUTURE MRA TRIALS IN HFrEF. FINALITY-HF (A Study to Evaluate Finerenone on Clinical Efficacy and Safety in Patients With Heart Failure Who Are Intolerant or Not Eligible for Treatment With Steroidal Mineralocorticoid Receptor Antagonists; NCT06033950) is a randomized, double-blind, placebo-controlled study to evaluate the efficacy of finerenone vs placebo in patients with HFrEF who are intolerant of or not eligible for treatment with steroidal MRAs (Figure 4). The study will enroll patients with NYHA functional class II-IV HF with ejection fraction <40% who are not on steroidal MRAs due to contraindication, ineligibility, or intolerance (defined as at least 1 episode of hyperkalemia, or an episode of worsening kidney function, or an episode of sexual side effects or hypotension, each leading to drug interruption or discontinuation). The primary endpoint is the time to the first occurrence of cardiovascular death or HF event. The results of FINALITY-HF will be important in broadening the evidence for the efficacy and safety of finerenone in patients with HFrEF with prior intolerance to steroidal MRAs.

FUTURE MRA TRIALS IN HFmrEF/HFpEF. The ongoing FINEARTS-HF (Study to Evaluate the Efficacy [Effect on Disease] and Safety of Finerenone on Morbidity [Events Indicating Disease Worsening] & Mortality [Death Rate] in Participants With Heart Failure and Left Ventricular Ejection Fraction [Proportion of Blood Expelled Per Heart Stroke] Greater or Equal to 40%; NCT04435626) is a randomized, double-blind, placebo-controlled trial evaluating the efficacy and safety of finerenone vs placebo in patients with NYHA functional class II-IV HF with an ejection fraction of ≥40% (Figure 3). The primary outcome is a composite of the between-group difference in the incidence of cardiovascular death and total HF events, defined as hospitalizations or emergency department visits for decompensated HF. Given the limited current evidence for the efficacy of MRAs in HFmrEF or HFpEF, FINEARTS-HF will

FIGURE 5 BalanceD-HF Trial


BalanceD-HF
Objective: Provide data on safety and efficacy of the early initiation of balcinrenone/AZD997 in patients with HFmrEF/HFpEF hospitalized due to acute HF
4800
patients
Inclusion Criteria:
• NYHA class III-V HF
• Recent HF event within 6 months
• NT-proBNP >300 pg/mL
• eGFR ≥ 20 to < 60 mL/min/1.73 m²
• Serum/plasma potassium ≥ 3.5 and ≤ 5.0 mmol/L
Exclusion Criteria:
• Acute coronary syndrome, stroke or transient ischemic attack within the previous 3 months
• Complex congenital heart disease
• Severe pulmonary disease
• Type 1 diabetes
• Kidney replacement therapy
• Hepatic disease
Primary Outcomes:
• Composite of death from any cause, number of HF events, time to first HF event, and changes in quality of life
• Number of serious adverse events
• Number of adverse events leading to discontinuation of study drug
1000
dapagliflozin 10mg
1000
balcinrenone/AZD997 15mg or 40mg + dapagliflozin 10mg

The BalanceD-HF trial (Study to Evaluate the Effect of Balcinrenone/Dapagliflozin in Patients With Heart Failure and Impaired Kidney Function) will evaluate the use of AZD997/balcinrenone in patients with HFmrEF or HFpEF who were recently hospitalized due to acute HF. Abbreviations as in Figure 1.

provide important evidence on the efficacy and safety of finerenone in patients with HFmrEF and HFpEF. The trial has finished enrollment and is expected to conclude in 2024.[40] FINEARTS-HF met its primary endpoint, achieving a statistically significant reduction of the composite of cardiovascular death and total (first and recurrent) HF events, defined as hospitalizations for HF or urgent HF visits.[41]

REDEFINE-HF (A Study to Determine the Efficacy and Safety of Finerenone on Morbidity and Mortality Among Hospitalized Heart Failure Patients; NCT06008197), is a randomized, double-blind,

TABLE 2 Future Steroidal MRA Clinical Trials

Trial Name	Drug Studied	Expected N	Inclusion Criteria	Primary Endpoints
SPIRIT-HF	Spironolactone vs placebo	1,300	NYHA functional class II or greater HF, LVEF ≥40%, NT-proBNP >300 pg/mL, controlled systolic blood pressure, and serum potassium <5.0 mmol/L	Cumulative number of primary composite events of cardiovascular death and total HF hospitalizations
SPIRRIT	Spironolactone + usual care vs usual care only	3,500	Stable heart failure signs/symptoms, class II-IV HF, LVEF ≥40%, NT-proBNP >300 ng/L	Incidence rate of cardiovascular deaths or HF hospitalizations
Polydiuretic Therapy for Heart Failure With Preserved Ejection Fraction: A Pilot Trial	Bumetanide + eplerenone + empagliflozin vs empagliflozin monotherapy	30	NYHA functional class II-IV HF, LVEF ≥50%, NT-proBNP levels >300 pg/mL	Feasibility of recruitment and compliance with the study protocol (30 participants and 80% participant completion of study protocol)

SPIRIT-HF (Spironolactone in the Treatment of Heart Failure), SPIRRIT (Spironolactone Initiation Registry Randomized Interventional Trial in Heart Failure With Preserved Ejection Fraction), and Polydiuretic Therapy for Heart Failure with Preserved Ejection Fraction are 3 ongoing/future clinical trials examining steroidal MRAs including spironolactone and eplerenone in heart failure with mildly reduced ejection fraction (HFmrEF) or heart failure with preserved ejection fraction (HFpEF). These trials will provide important data for the potential use of steroidal MRAs for this population following the mixed results seen in TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist).

Abbreviations as in Table 1.

placebo-controlled, event-driven trial to evaluate the efficacy of finerenone vs placebo for the treatment of patients hospitalized with HFmrEF or HFpEF (Figure 4). The eligibility criteria include those who are ≥18 years of age with current hospitalization or recent discharge with the primary diagnosis of HF, LVEF ≥40%, and NT-proBNP ≥1,000 pg/mL who are not treated with a MRA and do not have documented prior history of severe hyperkalemia in the setting of MRA use. The primary clinical and safety outcomes include the composite of total HF events and cardiovascular death, including HF hospitalizations, urgent visits for worsening HF, and cardiovascular deaths; the number of serious adverse events; and the number of adverse events leading to discontinuation of finerenone compared to placebo. The median follow-up period is expected to be 15 months, with a total anticipated duration of 30 months. This global and pragmatic trial will provide additional data on the efficacy and safety of the early initiation of finerenone in patients with HFmrEF/HFpEF who are hospitalized due to acute HF.

Although nonsteroidal MRAs are promising alternatives to steroidal MRAs due to the absence of side effects and potential efficacy for HFmrEF and HFpEF, the current research regarding steroidal MRAs also continues to grow (Table 2). SPIRIT-HF (Spironolactone in the Treatment of Heart Failure; NCT04727073) is a randomized, placebo-controlled, parallel-group phase 3 study that aims to determine the efficacy and safety of spironolactone in those with HFmrEF or HFpEF. Participants will include those who are ≥50 years of age who have NYHA functional class II or greater HF, LVEF ≥40%, NT-proBNP >300 pg/mL, controlled systolic blood pressure (defined as systolic blood pressure <140 mm Hg), and serum potassium <5.0 mmol/L. Participants will be randomized to receive either spironolactone 25 mg titrated up to 50 mg after 4 weeks or placebo and will be evaluated for a cumulative number of primary composite events of cardiovascular death and total HF hospitalizations. Although TOPCAT did not show a significant benefit of spironolactone compared with placebo in the overall cohort of patients with HFpEF, the potential benefit seen in the American cohort offers a rationale to study steroidal MRAs in those with HFpEF and HFmrEF. The results of SPIRIT-HF will be important in determining the efficacy and safety of spironolactone and other steroidal MRAs in this population.

The upcoming SPIRRIT (Spironolactone Initiation Registry Randomized Interventional Trial in Heart Failure With Preserved Ejection Fraction; NCT02901184) trial will provide additional evidence for the use of spironolactone for HFpEF through a registry-randomized clinical trial. This study will include patients in the Swedish Heart Failure Registry and the United States who have symptoms/signs of HF, elevated NT-proBNP, and LVEF ≥40%. Participants will be randomized to spironolactone + usual care vs usual care alone and will be analyzed for the incidence rate of cardiovascular death or HF hospitalization.

Similar to the CONFIRMATION-HF and MIRACLE trials, which will evaluate an MRA in combination with 1 or more treatments, Polydiuretic Therapy for Heart Failure With Preserved Ejection Fraction: A Pilot Trial (NCT05129722) will evaluate a steroidal MRA, eplerenone, in combination with a SGLT2 inhibitor, empagliflozin, and a loop diuretic, bumetanide, for the treatment of HFpEF. This Australian study will enroll participants ≥18 years of age with an established diagnosis of NYHA functional class II-IV

HF and LVEF ≥50% with NT-proBNP levels >300 pg/mL. Participants will be randomized to either a combination polypill consisting of bumetanide 0.5 mg, eplerenone 25 mg, and empagliflozin 10 mg or empagliflozin 10 mg monotherapy and will be evaluated for change in NT-proBNP, NYHA functional class, 6-minute walk test distance, and other measures of cardiorenal health from baseline to 4 weeks. Although primarily a feasibility study, this trial, along with CONFIRMATION-HF and MIRACLE, will provide evidence for using MRAs in conjunction with other HF medications and their potential synergy, contributing valuable insights to the evolving landscape of HF treatment.

LOOKING FORWARD

In addition to nonsteroidal MRAs such as finerenone and esaxerenone that have demonstrated potential HF benefit in humans, ocedurenone (KBP-5074) is a new nonsteroidal MRA that has demonstrated renoprotective effects in preclinical studies[42] and safety and efficacy in decreasing systolic blood pressure in patients with uncontrolled hypertension and stage 3b/4 CKD.[43] As a highly selective nonsteroidal MRA, ocedurenone offers a potential new treatment option for patients with CKD and resistant hypertension who may be unable to tolerate steroidal MRAs due to associated hyperkalemia; however, this drug has not been studied in a population with HF.

Although MRAs improve cardiac function by targeting the MR and inhibiting its downstream effects, recent research efforts have also targeted aldosterone synthase, a ligand of the MR, as a potential therapy for HF. By avoiding the MR, aldosterone synthase inhibitors have been thought to avoid the antiandrogenic- and progestogenic-related adverse effects seen with MRAs. Recent clinical trials have shown that aldosterone synthase inhibitors are effective in lowering blood pressure in healthy volunteers and patients with uncontrolled hypertension while avoiding antiandrogenic effects seen with MRAs;[44] however, the drug class has not been studied in patients with HF.

CONCLUSIONS

Despite current challenges to MRA implementation, such as the adverse effects including hyperkalemia and gynecomastia or breast pain and clinician doubt of late MRA initiation in long-term HFrEF patients, research regarding nonsteroidal MRAs such as finerenone and balcinrenone present a promising outlook for the greater use of MRAs, not only for HFrEF, but also for HFmrEF and HFpEF. Moreover, future trials examining spironolactone in those with HFpEF may offer more significant insights into the previous lack of benefit with spironolactone use found in the TOPCAT trial and may also raise the potential for the treatment of this population with steroidal MRAs.

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ADDRESS FOR CORRESPONDENCE: Dr Andrew Sauer, Saint Luke's Mid America Heart Institute, 4401 Wornall Road, Kansas City, Missouri 64111, USA. E-mail: asauer@saint-lukes.org. X handle: @AndrewJSauer.

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